REMARKS

Applicants thank the Examiner for the interview on July 1, 2005 in which the rejections of record were discussed. Potential amendments relating to the term "isolated" were addressed in the context of the rejection under 35 U.S.C. § 102. The written description and enablement rejections were further clarified by the Examiner. Potential amendments to address these rejections were also discussed.

Applicants respectfully request that should the claims not be deemed allowable in view of the amendments and arguments presented herein, the Examiner enter the amendments to the claims to reduce the issues on appeal.

With entry of the current amendment, claim 23 has been cancelled and claims 1, 19, and 30 have been amended. Claims 34 and 35 are withdrawn by the Examiner. Claims 1, 3-5, 19-22, 24, 26,30, 32, 33, 36, and 37 are therefore currently under consideration.

Claim 1 has been amended to recite an isolated nucleic acid that is separated from open reading frames that flank a menin gene in its naturally occurring state. This amendment adds no new matter. Support can be found, *e.g.,* on page 9, line 31 bridging to page 10, line 1; and page 10, lines 8-10.

Claim 19 has been amended to recite an oligonucleotide that binds to an exon or intron of a MEN1 gene as set forth in the claim. This amendment adds no new matter. Support can be found, *e.g.,* in claim 23 as filed.

Claim 30 has been amended to recite an isolated transfected cell. This amendment adds no new matter. Support can be found, *e.g.,* on page 23, lines 6-8.

The rejections will be addressed in the order set forth in the final Office Action mailed February 24, 2005.

Rejections under 35 U.S.C. § 112, first paragraph-enablement

Claims 1, 30, 32,-33, and 36-37 remain rejected on the basis of the Examiner's allegation that one of skill in the art would not know how to use nucleic acid sequences that

encode a protein having 95% identity to SEQ ID NO:2. Applicants note that claims 2 and 3 are not included in this rejection; thus, the basis of including claim 32 in this rejection is not clear.

In the rejection, the Examiner contends that one of skill would not know how to use the claimed sequences because the function of the protein is not known. In particular, the Examiner alleges that Applicants have provided no guidance in terms of mutations that abolish critical functions or domains. Applicants disagree with the Examiner for reasons of record. A biological role of the protein is in fact known: it plays a role in multiple endocrine neoplasia type 1 (MEN1) functioning as a tumor suppressor (*see, e.g.,* page 1, lines 1-3). Applicants have shown numerous mutations in all of the *MEN1* coding exons (2, 3, 4, 5, 6, 7, 8, 9, and 10) that lead to nonfunctional MEN1 alleles in patients having multiple endocrine neoplasia type 1. Furthermore, Applicants have identified three relatively common polymorphisms, one of which leads to a change in protein sequence, that were present in normal chromosomes. The Examiner provides no proper evidence or reasoning as to why one of skill would not be able to use the nucleic acids of the claimed scope, *e.g.,* for diagnostic purposes such as detecting normal or mutant *MEN1* nucleic acids, or to produce antibodies for the detection of normal and mutant menin proteins. Thus, the rejection does not establish that the claims aren't enabled. Applicants therefore respectfully request withdrawal of this rejection.

Claims 1, 3-5, 19-24, 26, 30, 32, 33, 36, and 37 also stand rejected under 35 U.S.C. § 112, first paragraph in view of the reasons set forth in section 5, page 3 of the final Office Action. The Examiner appears to believe that one of skill would not know how to use the claimed nucleic acids because the studies performed by Watout *et al.* in the article provided with Applicants' response mailed January 10, 2003, did not identify a change in level of expression of menin protein or cellular localization in lymphoblastoid cell lines from affected and non-affected individuals. Furthermore, the Examiner contends that one of skill would not know how to use the claimed nucleic acids because Guru *et al.* "1999" notes that the amino acid sequence of menin does not provide a clue to its cellular function. (Applicants note that this cite appears to

refer to Guru *et al.*, *Proc. Natl. Acad. Sci. USA* 95:1630-1634, 1998, submitted with Applicants' Feb 27, 2004.) Again, Applicants traverse this rejection for reasons of record.

First, Watout *et al*'s studies referred to above does not negate the fact that one of skill can use the claimed nucleic acid sequences, for example, to detect *MEN1* alleles or to generate diagnostic reagents to detect menin proteins. For example, a nucleic acid encoding SEQ ID NO:2 can be used as a probe for genomic DNA analysis directly to examine samples for a deletion in the *MEN1* gene. Applicants reiterate that the current invention is based on the discovery of a biological role for menin. Applicants teach that the gene *MEN1*, which encodes menin (exemplified by SEQ ID NO:2), is the underlying defect in multiple endocrine type neoplasia. The Examiner provides no evidence or reasoning as to why one of skill must know the precise cellular function of menin in order to be able to use the claimed nucleic acid sequences, for example, in the context of diagnosis. Accordingly, the rejection fails to establish a proper case that the claims are not enabled. Applicants therefore respectfully request withdrawal of this rejection.

Claims 3, 4, and 32 also remain separately rejected as allegedly lacking enablement. The Examiner contends that the claim encompass sequences in addition to SEQ ID NO:1 and SEQ ID NO:3 and that one of skill would therefore not know how to use the claimed nucleic acids. In order to expedite prosecution, Applicants have amended claim 1 to incorporate the definition of an isolated gene set forth in the specification. Applicants believe that the amendment to claim 1 obviates this rejection, as the claims do not read on expressing or using whole chromosomes.. Applicants therefore respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, first paragraph-written description

Claims 1, 30, 32-33, 36, and 37 remain rejected as allegedly lacking adequate written description support. The Examiner contends that an isolated nucleic acid encoding a polypeptide having at least 95% identity to SEQ ID NO:2 is not supported by proper written descriptive support in the specification. Although Applicants have identified menin-encoding

nucleic acids in the specification, *e.g.,* in Example 1 and Figures 3 and 4, the Examiner contends that the claims are not drawn to isolated or recombinant nucleic acids that are found to be mutated in patients, but rather are drawn to nucleic acid encoding variant menin polypeptides. The Examiner further contends that there is no correlation between the structural hallmark set forth in the claims and function of the claimed genus. Applicants disagree for reasons of record. Further, Applicants also note that the specification also discloses polymorphic variants, which are present in normal chromosomes, one of which results in a change in the protein sequence. It therefore is reasonable that one of skill could identify nucleic acids encoding polypeptides, mutant nor not, having at least 95% identity to SEQ ID NO:2 based on the written description in the specification. Additionally, the Examiner gives no reason as to why the claims could not encompass a nucleic acid encoding a variant menin polypeptide such as one of the mutant *MEN1* genes that encodes a menin protein having a missense mutation. As noted above, such nucleic acids can be used, *e.g.,* as diagnostic reagents, such as in identifying both normal and mutant *MEN1* genes.

With regard to the Examiner's allegation that there is no correlation between the structural hallmark and any function, as Applicants have pointed out, a structural element is set out in the instant claims, the reference sequence SEQ ID NO:2. There is in fact a correlation between this structural characteristic and a function: Applicants have shown that mutations in nucleic acids encoding SEQ ID NO:2 can lead to a disease, multiple endocrine neoplasia type 1. In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

Claims 19-24 and 26 were rejected as allegedly lacking adequate written description support. These claims are drawn to methods (and kits) for detecting mutant and normal *MEN1* alleles, *i.e.,* mutant and normal genes that encode menin (SEQ ID NO:2). The Examiner contends that the specification teaches only a single gene/cDNA that is mutated in multiple endocrine neoplasia-type 1 and this does not provide adequate written description of polynucleotides that encode SEQ ID NO:2 that are mutated or deleted so that one would be able

to predictably identify those included in the claimed genus. Applicants disagree for reasons of record.

Applicants have disclosed a wildtype *MEN1* allele and many mutated forms of *MEN1 (see, e.g.*, page 15, lines 13-17). Mutations occur in all of the coding exons (2-10). Furthermore, Applicants have identified polymorphism in the gene encoding SEQ ID NO:2 (*see, e.g.*, page 53, lines 4-6). Applicants have provided exemplary primers and probes that can be used to detect mutant and normal *MEN1* alleles (*see, e.g.*, exemplary primers and probes in Table 1 on page 18). Moreover, the specification confirms that those in the art can do precisely what the Examiner contends can't be performed predictably: Applicants identified numerous *MEN1* mutations in patients having multiple endocrine neoplasia type 1. In short, Applicants have disclosed many polynucleotide sequences encompassed by the genus set forth in the claims and illustrated that these can be readily detected. Thus, the specification provides proper written descriptive support. Applicants therefore respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. § 102

Claims 1, 3-5, 30, 32, 36, and 37 were rejected as allegedly anticipated. The Examiner contends that the term "isolated" encompasses human chromosome 11 present in a somatic cell hybrid panel disclosed in U.S. Patent No. 4,594,318. Applicants submit that this interpretation of claim 1 is incorrect in view of the complete definition of "isolated" provided in the specification. In order to expedite prosecution, however, Applicants have amended claim 1 to recite that the isolated nucleic acid is separated from open reading frames that flank a menin gene in its naturally occurring state. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

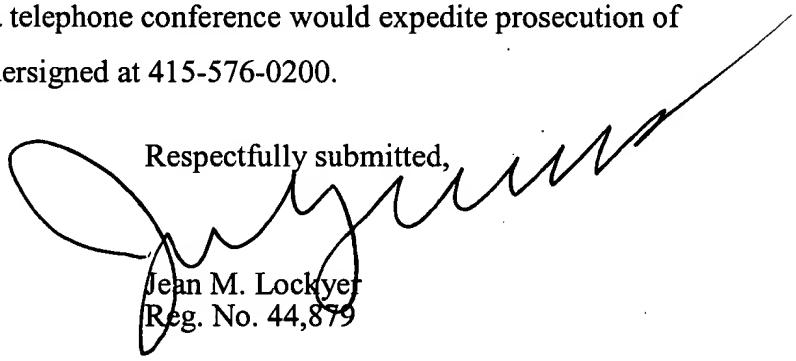
Claim 30 was rejected as allegedly indefinite in the recitation of a "transfected cell *in vitro*". In order to expedite prosecution, Applicants have amended the claim as suggested by the Examiner. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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